Benzyl Derivatives – Comments of Environmental Defense

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Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for Benzyl Derivatives.

The test plan for benzyl derivatives was prepared by the Flavor and Fragrance High Production Consortia. It proposes a category for 10 benzyl derivatives; these compounds are widely used in many flavors and fragrances and they are widely distributed in the food supply. They are also present as natural products in a number of foodstuffs. Thus, most people in the U.S. are exposed in one way or another to these chemicals, so it is important to evaluate if there is adequate screening level information on environmental fate and distribution, ecological effects and human health effects.

The test plan was very informative and well-written. However, the justification for a single category for all 10 members is marginal. It is based on the fact that all 10 members have similar metabolic pathways and to a much lesser extent on common toxicological properties. The fact that the chemicals are metabolized by the same enzymatic systems and, in some cases, have common degradation products does not necessarily mean that they share a common toxicological mechanism. For example, steroid hormones and polycyclic aromatic hydrocarbons are metabolized by the same enzymatic systems, yet the toxic effects that they cause are vastly different.

Likewise, the individual benzyl derivatives may interact with different receptor systems or other cellular constituents thereby causing distinct changes in gene expression. Thus, the benzyl derivatives might be excellent candidates to test in microarray gene expression technologies in order to better evaluate the scientific foundation for category formation. If all 10 proposed members caused the same pattern of gene expression changes in an appropriate in vitro or in vivo system, then these data coupled with data on physiochemical characteristics and toxic responses could provide a compelling justification for category formation, obviating the need for any additional testing.

Absent such microarry data or other convincing data, we do not believe that the existing data on reproduction and development endpoints are adequate to characterize the entire proposed category. Such data are available for only and two, respectively, of the proposed members have adequate data. In the case of reproductive toxicity, there are studies on benzaldehyde, benzyl acetate and methyl-2-hydroxybenzoate. These might be representative of three subcategories but the current database falls a bit short. In the case of developmental toxicity, data is only available for benzaldehyde and benzyl acetate. Accordingly, we urge that a developmental toxicity study be conducted on methyl-2-hydroxybenzoate and one additional member of the proposed category.

For other endpoints, the existing toxicological studies appear to be adequate. For example, adequate data exist for acute toxicity for all members, genetic toxicity for 9 members and repeat dose toxicity for 8 members. In the few cases where data are missing for these endpoints, the read-across extrapolation appears to be justified.

Thank you for this opportunity to comment.

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